PHOTOCURABLE GLYCOSAMINOGLYCAN DERIVATIVES, CROSSLINKED GLYCOSAMINOGLYCANS AND METHOD OF PRODUCTION THEREOF

FIELD OF THE INVENTION

The present invention relates to photocurable glycosaminoglycan derivatives each prepared by chemically binding a photoreactive compound to a glycosaminoglycan (hereinafter sometimes referred to as "GAG" for short), and crosslinked glycosaminoglycans having a three-dimensional network structure as obtained by subjecting said derivatives to photoreaction for dimerization of the photoreactive compound, to methods of preparing them and, further, to satisfactorily biocompatible materials for medical use which comprise the same.

BACKGROUND OF THE INVENTION

Photocurable resins comprising hydrophobic polymer systems to be subjected to photodimerization for crosslinking have so far been used in lithography, paints and printing, among others. On the contrary, there are few examples known where hydrophilic polymers are photocrosslinked.

On the other hand, attempts have been made to crosslink GAGs, which are typical hydrophilic polymers, by means of aldehydes, epoxy compounds, divinyl sulfone compounds and the like for prolonging the actions of GAGs in vivo or for preparing materials for medical use in the form of films or powders, for example for preventing tissue adhesion. However, since GAGs are macromolecules, the crosslinked GAG derivatives formed are still higher in molecular weight and this fact makes it difficult to completely remove unreacted materials and/or catalysts from the crosslinked GAG derivatives. Thus, when administered to or implanted into living bodies, said derivatives may frequently produce adverse effects, so that they are not suited for practical use. In addition, crosslinked GAG derivatives occur as gels or solids and therefore are difficult to mold after crosslinking, hence not suited for practical use. Furthermore, as for their use as carriers in sustained or controlled release drug preparations (JP-A-62-129226 corresponding to U.S. Pat. No. 5,128,326; the term "JP-A" used herein means an unexamined published Japanese patent application), sustained release of active ingredients can be attained only by taking advantage of the viscous property of crosslinked GAG derivatives and this disadvantage renders them unsuited for practical use. Thus, such methods and crosslinked GAG derivatives can hardly control the rate of release of drugs.

It is also known that photosensitive materials prepared by esterifying hydroxyl groups of microorganism or plant derived polysaccharides such as pullulan, amylose and mannan with cinnamoyl groups which are photodimerizable functional groups are usable as adsorbents, enzyme carriers or carriers for chromatography or in producing PS plates or photoresists or for other applications [JP-B-56-14969 corresponding to U.S. Pat. No. 3,960,685 (the term "JP-B" used herein means an examined published Japanese patent application), JP-A-60-219202].

However, the photosensitive materials mentioned above have a problem in securing safety, can hardly control cell adhesion and are poor in biocompatibility in humans and, therefore, they are not suited for use as medical materials to be directly applied to living bodies, in particular artificial organs, medical products to be used for covering wounds or in surgery, carriers in pharmaceutical preparations, or other materials to be used for some or other medical treatment.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide photocurable glycosaminoglycan derivatives and crosslinked glycosaminoglycans derived therefrom, which are highly safe and biocompatible.

Another object of the invention is to provide a method of preparing photocurable glycosaminoglycan derivatives readily moldable, when desired, for example by casting using a solvent, by which method unreacted substances causative of adverse effects, among others, can be readily eliminated, and a method of producing crosslinked GAGs therefrom.

A third object of the invention is to provide materials for medical use which are based on said photocurable GAG derivatives or crosslinked GAGs and are widely applicable for various purposes.

A fourth object of the invention is to provide nonadhesive materials comprising a crosslinked glycosaminoglycan which is not adherent to tissues but is biodegradable in accordance with the rate of wound healing and whose mechanical strength can be readily adjusted according to the mechanical stress at the site of application, and nonadhesive materials comprising a photocurable glycosaminoglycan derivative readily convertible to a crosslinked glycosaminoglycan upon irradiation with light in vivo.

A fifth object of the invention is to provide materials or preparations for realizing controlled drug release which comprise a crosslinked glycosaminoglycan and allow drug release at a rate suited for the drug included, entrapped or embedded therein and for the purpose of the drug application, as well as materials for realizing controlled drug release which comprise a photocurable glycosaminoglycan and are useful as carriers in the materials or preparations mentioned above or as starting materials therefor.

The present invention provides a photocurable glycosaminoglycan derivative (hereinafter sometimes referred to as "photocurable GAG" for short) which comprises a glycosaminoglycan and a photoreactive compound bound thereto, and a crosslinked glycosaminoglycan (hereinafter sometimes referred to as "crosslinked GAG" for short) prepared by subjecting said photocurable GAG to crosslinking reaction of said photoreactive compound. Said photocurable GAG can preferably be produced by subjecting hydroxyl or carboxyl groups of the glycosaminoglycan to esterification reaction with the photoreactive compound, by activating carboxyl groups of the glycosaminoglycan and subjecting the activated carboxyl groups to amidation reaction with the photoreactive compound, or by subjecting carboxyl groups of the glycosaminoglycan to amidation reaction with the photoreactive compound in the presence of a condensing agent. The crosslinked glycosaminoglycan can be produced by irradiating the photocurable GAG with light to thereby cause the crosslinking reaction of the photoreactive compound moieties one with another. Materials based on said crosslinked GAG are suited for medical use. The photocurable GAG, which gives said crosslinked GAG, can also serve as a material for medical use.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the ^{1}H-NMR spectrum used for bound cinnamic acid quantity determination in Example 1.

FIG. **2** shows UV/VIS spectra illustrating the attenuating absorbance at 279 nm as resulting from exposure to light in